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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,454	ROIZ ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *8-14,21-44 and 53-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15-20 and 45-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of group I, claims 1-7, 15-20 and 45-52, filed 10-14-03 in is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 8-14, 21-44 and 53-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonclected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the response filed 10-14-03.

Claims 1-60 are pending and claims 1-7, 15-20 and 45-52 are under consideration.

Priority

3. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must **include the relationship** (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the **first sentence of the specification** following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Specification

4. The abstract of the disclosure is objected to because the abstract should be on a separate paper alone but not a cover page of a WO publication. Correction is required. See MPEP § 608.01(b).

Information Disclosure Statement

5. The information disclosure statement filed 12-27-02 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. There is no copy of cited references Kawata et al, 1988, Irie et al., 1999 and Roiz et al., 2000, therefore, those references were not considered.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-7, 46-48 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "and/or" in claims 1, 46-48 and 52 is vague and renders the claims indefinite. It is unclear what is intended to be claimed. Changing the term "and/or" to "or...or both" would be remedial. Claims 2-7 depend on claim 1 but fail to clarify the indefiniteness.

8. Claims 1-7 and 45-52 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: whether the objective of the methods has been achieved, such as whether the tumor has been ameliorated, whether the tumor growth has been inhibited, and whether the number and size of the tumor have been reduced.

9. Claim 17 recites the limitation "wherein the abnormally proliferating cells are cancerous cells" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

10. Claim 18 recites the limitation "wherein the abnormally proliferating cells are cells" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-7, 15-20 and 45-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventively reducing the number of aberrant crypt foci (ACF) in a rat when RNase B1 is administered directly to the colon via osmotic micro-pump, or reducing the number of colon tumor, the tumor size, the number of ACFs or the tumor angiogenesis in a rat with oral administration of the RNase B1 microcapsules, and reducing the number and size of tumor, inhibiting the growth of tumor and reducing angiogenesis of tumor in rats treated with osmotic pumps that directly deliver the RNase B1 to the colon, does not reasonably provide enablement for a method of preventing, treating, inhibiting, or reversing

proliferation, colonization, differentiation or development of abnormally proliferating cells, such as tumor cells, in a subject by using any ribonuclease of the T2 family or its mutants that substantially lack ribonuclease activity via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-7, 15-20 and 45-52 are directed to a method of preventing, treating, inhibiting, or reversing proliferation or transformation to tumor, colonization, differentiation or development of abnormally proliferating cells, such as tumor cells, or reducing the size or number of tumors in a subject by using any ribonuclease of the T2 family, such as RNase T2, RNase Rh, RNase M, RNase Trv etc, and a pharmaceutical composition containing said ribonuclease. Claims 2 and 16 specify the ribonuclease of T2 family substantially lacks ribonucleolytic activity. Claims 4 and 18 specify the type of proliferating cells are associated with the cited proliferative disorders or diseases. Claim 5 specifies the administration route, including oral administration, topical administration, transmucosal administration, and parenteral administration etc. Claims 6 and 19 specify the ribonuclease is RNase B1.

The specification discloses that RNase B1 preventively administered via osmotic micro-pump reduces the number of aberrant crypt foci (ACF) in a rat, and RNase B1 preventively administered via oral administration of microcapsules reduces the number of colon tumor, the tumor size, the number of ACFs or the tumor angiogenesis in a rat, and the number and size of tumor are reduced, the growth of tumor is inhibited and angiogenesis of tumor is reduced in rats treated with osmotic pumps that directly deliver the RNase B1 to the colon (e.g. specification, example 4). The claims encompass preventing, treating, inhibiting, or reversing proliferation,

colonization, differentiation or development of abnormally proliferating cells, such as tumor cells, in a subject by using any ribonuclease of the T2 family or its mutants that substantially lack ribonucleolytic activity via various administration routes.

A pharmaceutical composition implies "therapeutic effects" of said pharmaceutical composition for a particular disease or disorder *in vivo*. The specification fails to provide adequate guidance and evidence that any member of T2 ribonuclease family or its mutants that substantially lack ribonucleolytic activity or a pharmaceutical composition comprising said ribonuclease can prevent, inhibit or reverse proliferation, colonization, differentiation or development of abnormally proliferating cells, or treat any abnormally proliferating cells, such as tumor cells, or reduce tumor number and size and tumor angiogenesis so as to provide therapeutic effect in a subject via various administration routes.

The state of the prior art for treating a disease with polypeptide *in vivo* was not well developed and was unpredictable at the time of the invention. Eck et al. 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reported that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors fro a successful gene therapy *in vivo*. Although Eck refers to the problems with gene therapy in vivo, however, it is also true for protein therapy in vivo that the amount of

protein that reach the target cells, the stability of the protein, the protein's compartmentalization within the cell, the type of target cells, the biological function of the protein, and the immune response of the host cells against the protein are all important factors that affect the efficiency of the protein treatment of various diseases. Further, it was known in the art that there are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids, and there is blood-brain barrier for treating brain tumors. Thus, administration route of the claimed ribonuclease is also an important factor that will determine whether the protein treatment of various abnormally proliferative cells associated with different disorders or diseases would provide therapeutic effects in vivo. The specification fails to provide adequate guidance and evidence how to administer sufficient ribonuclease of T2 family to target cells, such as brain tumor cells, renal cancer cells, or prostate cancer cells, via oral administration, cutaneous or subcutaneous administration, or intramuscular administration,

The specification states that "In rats fed with encapsulated RNase B1, the effect of the treatment was less significant than that obtained by osmotic pumps...a very small proportion of the protein reaches to the colon. As mentioned before, the microcapsules indeed pass the stomach, but they still have a long route through the small intestine and the cecum". The specification further indicates that "orally administered RNase B1 did not decrease the number and size of pre-existing tumors" (e.g. p. 51-52). Therefore, administration route of the protein plays an important role in the efficiency of delivering the protein to target cells and providing

therapeutic effects in vivo but the specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed.

Further, mechanism of the ribonuclease of T2 family on the inhibition of the abnormally proliferating cells, such as cancer cells, is unknown. The specification of the present application indicates that the binding of the RNaseB1 to actin but not the ribonucleolytic activity of the ribonuclease plays a role in the inhibition of germination or pollen tube growth. Different member of the T2 ribonuclease family would have distinct protein sequences and different biological functions. There is not evidence of record that member of the ribonuclease of T2 family other than RNase B1 would also bind to actin such that said ribonuclease could inhibit the germination or pollen tube growth, or reduce the clonogenicity of the cancer cells *in vitro* and *in vivo*. The specification fails to provide what region of the ribonuclease protein of T2 family contributes to the anti-proliferation, anti-differentiation, anti-transformation, and anti-tumor activity of RNase B1 in vitro or in vivo.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma

protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of the unpredictability of protein therapy and the biological function of a protein from mere amino acid sequence, and the lack of information regarding the structural feature that contributes to the claimed RNase anti-tumor and anti-proliferation activities etc., one skilled in the art at the time of the invention would not know how to use the claimed ribonuclease of T2 family or its mutants that substantially lack ribonucleolytic activity or a pharmaceutical composition comprising said ribonuclease to prevent, inhibit or reverse proliferation, colonization, differentiation or development of abnormally proliferating cells, or to treat any abnormally proliferating cells, such as tumor cells, or to reduce tumor number and size and tumor angiogenesis so as to provide therapeutic effect in a subject via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the

breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 15, 17, 18 and 20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Ohgi et al., 1991 (J. Biochem., Vol. 109, p. 776-785).

Claims 15, 17, 18 and 20 are directed to a pharmaceutical composition comprising a ribonuclease of the T2 family, such as RNase Rh, and a pharmaceutically acceptable carrier.

Ohgi teaches construction of a vector containing RNase Rh cDNA, transfection of yeast host cells with said vector, and purification of the recombinant RNase Rh protein from said yeast host cells (e.g. p. 777). The buffer solution containing the purified RNase Rh protein is considered a pharmaceutically acceptable carrier. Thus, claims 15, 17, 18 and 20 are clearly anticipated by Ohgi.

It should be noted that the term "pharmaceutical" does not carry weight when a 102 or 103(a) rejection are being considered.

15. Claims 1, 2, 6 and 15-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Roiz et al., 1995 (Int. J. Plant Sci., Vol. 156, No. 1, p. 37-41, IDS).

Claims 1, 2, 6 and 15-20 are directed to a method of inhibiting proliferation, differentiation, or development of abnormally proliferating cells in a subject by using any ribonuclease of the T2 family, such as RNase B1, and a pharmaceutical composition containing said ribonuclease and a pharmaceutically acceptable carrier. Claims 2 and 16 specify the ribonuclease of T2 family substantially lacks ribonucleolytic activity.

Roiz teaches preparing stigmatic RNase protein, which is RNAse B1 as indicated in the specification of the present application on page 9 lines 33-35, by soaking stigmas in 20mM Tris-HCl buffer to allow proteins to diffuse into the buffer, the proteins were separated on SDS-PAGE gel, and individual protein band was dissected and submerged into the germinating tubes. Roiz shows that the 21 kD stigmatic RNase (RNase B1) and pancreatic RNase A significantly inhibit pollen germination and pollen tube length, i.e. RNase B1 inhibit proliferation or development of abnormally proliferating cells in a subject (pollen) (e.g. abstract, p. 38). The SDS-PAGE gel will denature the RNase B1 protein and substantially inactivate its ribonucleolytic activity. The buffer solution containing the RNase B1 is considered a pharmaceutically acceptable carrier. Thus, claims 1, 2, 6 and 15-20 are anticipated by Roiz.

It should be noted that the term "pharmaceutical" does not carry weight when a 102 or 103(a) rejection are being considered.

16. Claims 15-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawada et al., 1990 (Eur. J. Biochem., Vol. 187, p. 255-262).

Claims 15-18 and 20 are directed to a pharmaceutical composition comprising a ribonuclease of the T2 family, such as RNase T2, or a ribonuclease substantially lacks ribonucleolytic activity, and a pharmaceutically acceptable carrier.

Kawata teaches dissolving RNase T2 protein in 0.1 M citrate buffer solution at various pH and adding diethyl pyrocarbonate in 10% dioxane to the solution so as to inactivate RNase ribonucleolytic activity (e.g. abstract, p. 255, right column). The buffer solution containing the RNase T2 protein or inactivated RNase T2 protein is considered pharmaceutically acceptable carrier.

It should be noted that the term "pharmaceutical" does not carry weight when a 102 or 103(a) rejection are being considered.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.